2.0 SYNOPSIS

Name of Sponsor/Company: BIAL - Portela & C[a], S.A.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
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Title of Study: Efficacy and safety of BIA 9-1067 in idiopathic Parkinson's disease patients with "wearing-off" phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical study.		
Protocol number (study name): BIA-91067-302 (BIPARK II)		
Coordinating Investigator: Professor Andrew Lees, MD, FRCP, FMedsCI, National Hospital for Neurology and Neurosurgery, Queens Square, London, WC1N 3BG, UK.		
Study center(s): 71 investigational sites in 12 countries (Argentina, Australia, Belgium, Chile, Czech Republic, Estonia, India, Israel, South Korea, Russia, South Africa and United Kingdom)		
Publication (reference): None.		
Studied double-blind period (years): 18 March 2011 (First subject, first visit) to 11 July 2012 (Last subject, last visit).	**Phase of development:** III	
Objectives: The primary objective was to investigate the efficacy of two different doses of opicapone (OPC) (25 mg and 50 mg), administered once daily, compared with placebo, when administered with the existing treatment of levodopa (L-DOPA) plus a DDCI, in subjects with Parkinson's disease (PD) and end-of-dose motor fluctuations. The secondary objective was to investigate the safety and tolerability of OPC in comparison to placebo when administered with the existing treatment of L-DOPA/DDCI.		
Methodology: The study was designed to include two periods, a double-blind (DB) period and an open-label (OL) period. This study report only covers the results of the DB period. The results of the OL extension period are presented in a separate report. This was a multicenter, DB, randomized, placebo controlled, parallel group study to investigate two different doses of OPC, given orally for 14 to 15 weeks, in comparison with matching placebo, in subjects with idiopathic PD who were already receiving L-DOPA/DDCI therapy. After a screening period of up to two weeks, subjects entered a 14- to 15-week DB period, followed by an additional one year OL extension period in which all subjects were treated with OPC. Eligible subjects were		

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randomly assigned to one of the three treatments at Visit (V2) using a 1:1:1 ratio. Study medication was administered in combination with existing treatment of L-DOPA/ DDCI. From V2 to V4 of the DB period (first 2-3 weeks of DB period), the Investigator could decrease the daily dose of L-DOPA (keeping the number of daily intakes unchanged), according to subject response. If needed, the L-DOPA dose could be increased again up to the baseline dose level. The dosage of L-DOPA was not to be changed during the study from V4 through to the end of the DB period. After completion of this maintenance period, subjects who did not enter the OL period were to have a post-study visit in 14 days. No new anti-PD drug was to be started during the study and any that were ongoing at the start of the study were to be kept at a stable dose for at least four weeks before screening and throughout the study.

Number of subjects (planned and analyzed):
It was planned to randomize 405 subjects to achieve 135 subjects in each of the three treatment groups.
Consented: 485 subjects.
Randomized: 427 subjects.
Analyzed safety set (SS): 411 subjects.
Analyzed full analysis set (FAS): 407 subjects.

Diagnosis and main criteria for inclusion:
Male and female subjects between 30 and 83 years old, inclusive, who had a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for at least three years, with the presence of recognizable ON and OFF states (motor fluctuations) and an average total daily OFF-time while awake of at least 1.5 hours. The disease severity at ON had to be rated as Stages I-III using the modified Hoehn &Yahr staging of PD and subjects were to have been treated with L-DOPA/DDCI (three to eight daily doses, which could include a slow-release formulation) for at least one year with clear clinical improvement.
Subjects with a dyskinesia disability score >3 in the Unified Parkinson's Disease Rating Scale (UPDRS) Sub-section IV A, item 33 were not permitted to enter the study, neither were subjects with severe and/or unpredictable OFF periods.

Test product, dose and mode of administration, batch number:
25 mg OPC capsules for oral administration once daily.
50 mg OPC capsules for oral administration once daily
For batch numbers, see Appendix 16.1.6.
The investigational medicinal product (IMP) was to be taken in the evening and administered at least one hour after the last daily dose of L-DOPA/DDCI. Subjects had to fast for one hour before and for at least one hour after intake of IMP.

Duration of treatment:
Total duration of the DB treatment for an individual subject was 14 to 15 weeks. At the end of the DB period, subjects could enter a 1-year open-label extension in which all subjects were to be

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treated with OPC. The total duration of treatment for an individual subject in this study was therefore up to 67 weeks.

Reference therapy, dose and mode of administration, batch number:
Matching placebo capsules for oral administration. For batch numbers, see Appendix 16.1.6.

Criteria for evaluation:
Efficacy:
Subject diary charts for ON/OFF periods; UPDRS Sections I (ON), II (ON and OFF), III (ON), IV, V (ON), VI (ON and OFF); change in L-DOPA/DDCI dose; Investigator's and subject's assessments of change; Parkinson's Disease Sleep Scale (PDSS); Parkinson's Disease Questionnaire-39 (PDQ-39); Non-motor Symptoms Scale (NMSS).
Safety:
Adverse events (AEs), laboratory safety tests, physical and neurological examinations, skin examination for screening of melanoma, vital signs, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS) and modified Minnesota Impulsive Disorders Interview (mMIDI).

Statistical methods:
Primary efficacy analysis:
The primary efficacy parameter, change from baseline in absolute OFF-time at the end of the DB period (V7), was analyzed using an analysis of covariance (ANCOVA) model with treatment group and pooled country as fixed effects and baseline OFF-time as a covariate, and a last post-baseline observation carried forward (LOCF) approach. Differences between each OPC dose group (25 mg and 50 mg) and the placebo group were estimated from the model.
Secondary efficacy analysis:
An ANCOVA similar to that used for analyzing the primary efficacy variable was used for all relevant secondary efficacy variables in the DB period.
Responder rates were compared between the different treatment groups in the DB period, using a Cochran-Mantel-Haenszel test with pooled country as strata. A non-parametric van Elteren's test for treatment effect, stratified by pooled country, was performed for the analysis of the Investigator's and Subject's global assessment of change scores at the end of the DB period.
Safety analysis:
All safety parameters were presented by descriptive statistics for each treatment group. The analyses focused on treatment-emergent AEs (TEAEs) and were categorized by System Organ Class (SOC) and Preferred Term (PT). Serious TEAEs, TEAEs leading to death and TEAEs resulting in discontinuation of IMP were tabulated using frequency tables. For laboratory parameters, descriptive analyses at each time point and of changes from baseline to each post-baseline time point were presented by treatment group. Values of vital signs and 12-lead ECGs, including changes from baseline were summarized. Frequency tables and subject listings were to be presented for markedly abnormal values. Shift tables were to be presented according to the reference ranges (low, normal or high).

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Sample size calculation:

In previous studies on catechol-O-methyltransferase inhibitors a mean change in daily OFF-time between approximately 60 and 145 minutes relative to a placebo effect of approximately 30 minutes and a common standard deviation of approximately 150 minutes were reported (e.g. study BIA-3202-202).

It was assumed that the mean reductions in OFF-time were 90- and 105-minutes for the two different OPC doses and 30 minutes for the placebo. A sample size of 135 subjects per treatment group in the FAS was calculated to ensure a marginal power of more than 95% to confirm a treatment effect in the most efficacious group and a marginal power of about 85% to confirm a treatment effect in the less efficacious dose.

Summary of results:

Efficacy Results:

The primary efficacy variable was the change from baseline in absolute OFF-time at the end of the DB period (V7) and was analyzed using the FAS as the primary analysis population. Mean reduction in absolute OFF-time for both the 25 and 50 mg OPC groups was considerably greater than in the placebo group. The changes from baseline in absolute OFF-time were (LS means) -64.46 mins for placebo, -101.67 mins for OPC 25 mg and -118.77 mins for OPC 50 mg. The difference was -37.21 mins (P = 0.1061) for the comparison between OPC 25 mg and placebo, and -54.31 mins (P = 0.0081) for the comparison between OPC 50 mg and placebo. Based on the adjusted P-values, the difference from placebo was statistically significant for the OPC 50 mg group but did not reach statistical significance for the OPC 25 mg group. Similar results were observed for the PP set, with LS means of -67.58 mins for placebo, -98.06 mins for OPC 25 mg and -128.17 mins for OPC 50 mg.The results of sensitivity analyses were comparable in terms of the direction and magnitude of effect sizes to the primary LOCF analysis, and collectively support its results. Sensitivity analyses have been presented to cater for the non-conservative estimates for missing data that LOCF method provides (the assumption that data after a subject drops out is constant) and further analyses have been presented to test the different assumptions about the missing data. Consistent treatment effects were seen across all of the sensitivity analyses. The results from diary-derived secondary efficacy endpoints also lent support to the primary analysis. The proportion of OFF-time responders was 62.4% (P = 0.0405) in the OPC 25 mg group and 66.0% (P = 0.0088) in the OPC 50 mg group. For the percentage OFF-time, the LS means for the change from baseline compared to placebo were -4.31% (P = 0.0297) for OPC 25 mg and -5.46% (P = 0.0042) for OPC 50 mg. Additionally, subject diaries revealed an accompanying increase in daily ON-time in the active groups, ranging between 45.42 mins (P = 0.0204) for OPC 25 mg and 52.59 mins (P = 0.0051) for OPC 50 mg. These improvements were mostly due to an increase of ON-time with non-troublesome dyskinesia: 39.55 mins (P = 0.0670) for OPC 25 mg and 40.84 mins for OPC 50 mg (P = 0.0480). The changes in the ON-time with troublesome dyskinesia were not significant for both OPC groups: 8.20 mins (P = 0.4898) for OPC 25 mg and 14.41 mins (P = 0.2060) for OPC 50 mg. Overall, mean

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scores for disease and symptom scales (UPDRS, PDSS, PDQ-39 and NMSS) showed slight improvements in all treatment groups with no significant differences between them. The results of the different subgroup analyses were overall consistent with the primary results, suggesting that OPC was effective in decreasing OFF-time regardless of age, gender, disease duration or severity, or use of other anti-PD drugs.

Safety results:

The majority (≥64.0%) of subjects in each treatment group experienced at least one TEAE. The overall incidence of TEAEs was comparable in the OPC 25 mg (69.6%) and OPC 50 mg (72.0%) groups, and slightly higher than in the placebo group (64.0%). The most common TEAEs occurring in OPC groups compared to placebo were dyskinesia (24.0% vs. 8.1%), constipation (8.0% vs. 1.5%), and dry mouth (6.9% vs. 0.7%). Other dopaminergic events such as hallucinations and orthostatic hypotension were reported in few subjects (<3.5%), but a higher incidence was observed in OPC groups. The incidence of somnolence, sleep disorders, impulse control disorders and depressive events was similar across OPC and placebo groups. Urine discoloration was reported for only one (0.8%) subject under OPC treatment. The majority of TEAEs were mild or moderate in intensity. Severe TEAEs were reported in few subjects and in similar proportions across OPC and placebo groups. There was one death reported during the treatment period: one case of pneumonia (placebo). One additional subject died during the screening period as a result of a myocardial infarction (screening failure). Serious TEAEs were observed in 18 (4.4%) subjects overall. Although more subjects reported serious adverse events (SAEs) in the OPC 50 mg group (6.0% OPC 50 mg compared to 3.2% OPC 25 mg and 3.7% placebo) there were no discernible differences in the types of events among the three treatment groups and no dose-related trends were evident. No cardiovascular or cerebrovascular SAEs were reported, nor SAEs related to hepatic toxicity. No melanoma cases were observed. Discontinuations due to TEAEs were more frequent for OPC 50 mg (11.3%) than for OPC 25 mg (4.0%) or placebo (6.6%). The most common reported TEAE leading to discontinuation in the OPC groups was dyskinesia. The incidence of other TEAEs leading to study discontinuation was low (≤2% of subjects). No subject discontinued due to diarrhea. For the majority of laboratory parameters there were no substantial changes across visits for both OPC groups and placebo. A trend was observed in OPC groups towards slightly decreased hemoglobin levels and increased blood creatine phosphokinase (CPK). However, the related AEs (anemia and increased blood CPK) were reported in similar incidences across OPC groups and placebo and most cases were mild or moderate in intensity, which indicates those laboratory findings were generally of little clinical relevance. There were no relevant findings for liver function tests: there was one single post-baseline report of alanine aminotransferase (ALT) ≥3xupper range limit (URL) (3.5xURL; OPC 50 mg); there were no cases of bilirubin elevation ≥2xURL. Importantly, there were no potential Hy's law cases. There were small changes in all neurological and physical examination findings during the study and no differences between groups were evident. Overall, the mean and mean changes from baseline for vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, and body weight) were not substantially

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different across visits for OPC and placebo groups. Overall, the means and mean changes from baseline for ECG parameters (heart rate PR, QRS, QT, QTc) were not substantially different across visits for the active treatment groups and placebo. Pre-specified ECG abnormalities were found in approximately the same proportion of subjects across all groups and were overall not significant. No differences between OPC groups and placebo were observed for any of the C-SSRS parameters. No subject committed suicide, attempted suicide or had other suicidal behavior.Impulsive disorders as screened with the mMIDI and review of TEAEs were reported in few subjects: 5 subjects in the OPC 50 mg group and 2 subjects in the placebo group.

Conclusions:

OPC was effective at reducing OFF-time in PD patients with motor fluctuations. The OPC 50 mg dose was statistically significantly different from placebo with respect to the primary efficacy endpoint. The OPC 25 mg dose did not reach statistical significance over placebo, but a trend towards greater reductions of OFF-time was observed. OPC was safe and well tolerated at both doses.